SUPPORTING MATERIAL

Coordination of miR-192 and miR-22 in p53-mediated cell fate decision

Here, we present the ordinary differential equations for the model and standard parameter values and the initial values of variables .

Supplemental Method S1: Ordinary Differential Equations for the Model

$$\frac{d[\mathrm{p53}^*]}{dt} = k_{\mathrm{acp53}}[\mathrm{p53}] - k_{\mathrm{dep53}}[\mathrm{p53}^*] - k_{\mathrm{dp53p}}[\mathrm{Mdm2_n}]\frac{[\mathrm{p53}^*]}{[\mathrm{p53}^*] + j_{\mathrm{1p53n}}} \quad (1)$$

$$\frac{d[\mathrm{p53}]}{dt} = k_{\mathrm{sp53}} - k_{\mathrm{dp53n}}[\mathrm{p53}] + k_{\mathrm{dep53}}[\mathrm{p53}^*] - k_{\mathrm{acp53}}[\mathrm{p53}] - k_{\mathrm{dp53}}[\mathrm{Mdm2_n}]\frac{[\mathrm{p53}]}{[\mathrm{p53}] + j_{\mathrm{1p53n}}} \quad (2)$$

$$k_{\mathrm{acp53}} = k_{\mathrm{acp530}} + k_{\mathrm{acp531}}\frac{\mathrm{DD}}{\mathrm{DD} + j_{\mathrm{DDp53}}} \quad (3)$$

$$k_{\mathrm{dmdm2n}} = k_{\mathrm{dmdm2n0}} + k_{\mathrm{dmdm2n1}}\frac{\mathrm{DD}}{\mathrm{DD} + j_{\mathrm{DDm2}}} \quad (4)$$

$$\frac{d[\mathrm{mdm2m}]}{dt} = k_{\mathrm{smdm2m0}} + k_{\mathrm{smdm2m}}\frac{[\mathrm{p53}^*]^4}{[\mathrm{p53}^*]^4 + j^4_{\mathrm{smdm2m}}} - k_{\mathrm{dmdm2m}}[\mathrm{mdm2m}] \quad (5)$$

$$\frac{d[\mathrm{Mdm2_n}]}{dt} = k_{\mathrm{i}}[\mathrm{Mdm2_{cp}}] - k_{\mathrm{o}}[\mathrm{Mdm2_n}] - k_{\mathrm{dmdm2n}}[\mathrm{Mdm2_n}] \quad (6)$$

$$\frac{d[\mathrm{Mdm2_c}]}{dt} = k_{\mathrm{tmdm2}}[\mathrm{mdm2m}] - k_{\mathrm{dmdm2c}}[\mathrm{Mdm2_c}] + k_{\mathrm{dpmdm2}}\frac{[\mathrm{Mdm2_{cp}}]}{[\mathrm{Mdm2_{cp}}] + j_{\mathrm{dpmdm2}}} - k_{\mathrm{pmdm2}}[\mathrm{Akt_p}]\frac{[\mathrm{Mdm2_c}]}{[\mathrm{Mdm2_c}] + j_{\mathrm{pmdm2}}} \quad (7)$$

$$k_{\mathrm{tmdm2}} = \frac{k_{\mathrm{tmdm20}}}{[\mathrm{miR\text{-}192}] + j_{\mathrm{DDm2}}} \quad (8)$$

$$\frac{d[\mathrm{Mdm2_{cp}}]}{dt} = k_{\mathrm{pmdm2}}[\mathrm{Akt_p}]\frac{[\mathrm{Mdm2_c}]}{[\mathrm{Mdm2_c}] + j_{\mathrm{pmdm2}}} - k_{\mathrm{dpmdm2}}\frac{[\mathrm{Mdm2_{cp}}]}{[\mathrm{Mdm2_{cp}}] + j_{\mathrm{dpmdm2}}} - k_{\mathrm{i}}[\mathrm{Mdm2_{cp}}] + k_{\mathrm{o}}[\mathrm{Mdm2_n}] - k_{\mathrm{dmdm2c}}[\mathrm{Mdm2_{cp}}] \quad (9)$$

$$\frac{d[\text{miR-192}]}{dt} = k_{\text{smiR1920}} + k_{\text{smiR192}} \frac{[\text{p53}^*]^4}{[\text{p53}^*]^4 + j_{\text{smiR192}}^4} - k_{\text{dmiR192}}[\text{miR-192}] \tag{10}$$

$$\frac{d[\text{Akt}_\text{p}]}{dt} = k_{\text{acakt}}[\text{PIP3}] \frac{[\text{Akt}]}{[\text{Akt}] + j_{\text{acakt}}} - k_{\text{deakt}} \frac{[\text{Akt}_\text{p}]}{[\text{Akt}_\text{p}] + j_{\text{deakt}}} \tag{11}$$

$$[\text{Akt}] = \text{Akt}_{\text{tot}} - [\text{Akt}_\text{p}] \tag{12}$$

$$\frac{d[\text{PIP3}]}{dt} = k_{\text{p2}} \frac{[\text{PIP2}]}{[\text{PIP2}] + j_{\text{p2}}} - k_{\text{p3}}[\text{PTEN}] \frac{[\text{PIP3}]}{[\text{PIP3}] + j_{\text{p3}}} \tag{13}$$

$$[\text{PIP2}] = \text{PIP}_{\text{tot}} - [\text{PIP3}] \tag{14}$$

$$\frac{d[\text{PTEN}]}{dt} = k_{\text{sPTEN0}} + k_{\text{sPTEN}} \frac{[\text{p53}^*]^4}{[\text{p53}^*]^4 + j_{\text{sPTEN}}^4} - k_{\text{dPTEN}}[\text{PTEN}] \tag{15}$$

$$\frac{d[\text{p21m}]}{dt} = k_{\text{sp21m0}} + k_{\text{sp21m}} \frac{[\text{p53}^*]^4}{[\text{p53}^*]^4 + j_{\text{sp21m}}^4} - k_{\text{dp21m}}[\text{p21m}] \tag{16}$$

$$\frac{d[\text{p21}_{\text{tot}}]}{dt} = k_{\text{tp21}}[\text{p21m}] - k_{\text{dp21}}[\text{p21}_{\text{tot}}] \tag{17}$$

$$k_{\text{tp21}} = \frac{k_{\text{tp210}}}{[\text{miR-22}] + j_{\text{22p21f}}} \tag{18}$$

$$k_{\text{dp21m}} = k_{\text{dp21m0}} + k_{\text{dp21m1}} \frac{[\text{miR-22}]}{[\text{miR-22}] + j_{\text{22p21d}}} \tag{19}$$

$$\frac{d[\text{miR-22}]}{dt} = k_{\text{smiR220}} + k_{\text{smiR22}} \frac{[\text{p53}^*]^4}{[\text{p53}^*]^4 + j_{\text{smiR22}}^4} - k_{\text{dmiR22}}[\text{miR-22}] \tag{20}$$

$$\begin{aligned} \frac{d[\text{p21CE}]}{dt} &= k_{\text{asp21ce}}[\text{p21}][\text{CycE}] - k_{\text{dsp21ce}}[\text{p21CE}] \\ &\quad -(k_{\text{dp21}} + k_{\text{dcyce}})[\text{p21CE}] \end{aligned} \tag{21}$$

$$[\text{p21}] = [\text{p21}_{\text{tot}}] - [\text{p21CE}] \tag{22}$$

$$\frac{d[\text{CycE}_{\text{tot}}]}{dt} = k_{\text{scyce0}} + k_{\text{scyce}} \frac{[\text{E2F1}]^2}{[\text{E2F1}]^2 + j_{\text{scyce}}^2} - k_{\text{dcyce}}[\text{CycE}_{\text{tot}}] \tag{23}$$

$$[\text{CycE}] = [\text{CycE}_{\text{tot}}] - [\text{p21CE}] \tag{24}$$

$$\begin{aligned} \frac{d[\text{E2F1}]}{dt} &= k_{\text{se2f1}} - k_{\text{asre}}[\text{Rb}][\text{E2F1}] + k_{\text{dsre}}[\text{RE}] \\ &\quad + k_{\text{prb}}[\text{CycE}] \frac{[\text{RE}]}{[\text{RE}] + j_{\text{prb}}} - k_{\text{de2f1}}[\text{E2F1}] \end{aligned} \tag{25}$$

$$\frac{d[\text{E2F1}_{\text{tot}}]}{dt} = k_{\text{se2f1}} - k_{\text{de2f1}}[\text{E2F1}_{\text{tot}}] \tag{26}$$

$$k_{\text{de2f1}} = k_{\text{de2f10}} + k_{\text{de2f11}} \frac{j_{\text{DD2f}}}{j_{\text{DD2f}} + \text{DD}} \tag{27}$$

$$[\text{RE}] = [\text{E2F1}_{\text{tot}}] - [\text{E2F1}] \tag{28}$$

$$\frac{d[\mathrm{Rb_p}]}{dt} = k_{\mathrm{prb}}[\mathrm{CycE}]\frac{[\mathrm{Rb}]}{[\mathrm{Rb}] + j_{\mathrm{prb}}} - k_{\mathrm{dprb}}\frac{[\mathrm{Rb_p}]}{[\mathrm{Rb_p}] + j_{\mathrm{dprb}}} + k_{\mathrm{prb}}[\mathrm{CycE}]\frac{[\mathrm{RE}]}{[\mathrm{RE}] + j_{\mathrm{prb}}} \quad (29)$$

$$[\mathrm{Rb}] = [\mathrm{Rb_{tot}}] - [\mathrm{Rb_p}] - [\mathrm{RE}] \quad (30)$$

$$\frac{d[\mathrm{Bax}]}{dt} = k_{\mathrm{sbax0}} + k_{\mathrm{sbax}}\frac{[\mathrm{p53^*}]^4}{[\mathrm{p53^*}]^4 + j_{\mathrm{sbax}}^4} - k_{\mathrm{dbax}}[\mathrm{Bax}] \quad (31)$$

$$\frac{d[\mathrm{CytoC}]}{dt} = (k_{\mathrm{accytoc0}} + k_{\mathrm{accytoc1}}[\mathrm{Bax}]\frac{[\mathrm{Casp3}]^4}{[\mathrm{Casp3}]^4 + j_{\mathrm{cap3bx}}^4})(\mathrm{CytoC_{tot}} - [\mathrm{CytoC}]) - k_{\mathrm{decytoc}}[\mathrm{CytoC}] \quad (32)$$

$$\frac{d[\mathrm{Apaf1}]}{dt} = k_{\mathrm{sapaf10}} + k_{\mathrm{sapaf1}}\frac{[\mathrm{E2F1}]^2}{[\mathrm{E2F1}]^2 + j_{\mathrm{sapaf1}}^2} - k_{\mathrm{dapaf1}}[\mathrm{Apaf1}] \quad (33)$$

$$\frac{d[\mathrm{Apops}]}{dt} = k_{\mathrm{acapops}}(([\mathrm{CytoC}] - 7[\mathrm{Apops}])([\mathrm{Apaf1}] - 7[\mathrm{Apops}]))^7 - k_{\mathrm{deapops}}[\mathrm{Apops}] \quad (34)$$

$$\frac{d[\mathrm{Casp9}]}{dt} = (k_{\mathrm{accasp90}} + k_{\mathrm{accasp91}}\frac{[\mathrm{Casp3}]^4}{[\mathrm{Casp3}]^4 + j_{\mathrm{casp3}}^4}\,\frac{[\mathrm{Apops}]^4}{[\mathrm{Apops}]^4 + j_{\mathrm{apops}}^4})(\mathrm{Casp9_{tot}} - [\mathrm{Casp9}]) - k_{\mathrm{decasp9}}[\mathrm{Casp9}] \quad (35)$$

$$\frac{d[\mathrm{Casp3}]}{dt} = (k_{\mathrm{accasp30}} + k_{\mathrm{accasp31}}\frac{[\mathrm{Casp9}]^4}{[\mathrm{Casp9}]^4 + j_{\mathrm{casp9}}^4})(\mathrm{Casp3_{tot}} - [\mathrm{Casp3}]) - k_{\mathrm{decasp3}}[\mathrm{Casp3}] \quad (36)$$

Supplemental Table S1: Variables and their initial values

Variable	initial values	Variable	initial values	Variable	initial values	Variable	initial values
$[\mathrm{p53^*}]$	0.0009	[miR-192]	0.1	[miR-22]	0.1	[Bax]	0.1
[p53]	0.0343	$[\mathrm{Akt_p}]$	0.9415	[p21CE]	0.08	[CytoC]	0.197
[mdm2m]	0.05	[PIP3]	0.8944	$[\mathrm{CycE_{tot}}]$	0.166	[Apaf1]	0.01
$[\mathrm{Mdm2_n}]$	0.6413	[PTEN]	0.1	[E2F1]	0.1	[Apops]	0
$[\mathrm{Mdm2_c}]$	0.0314	[p21m]	0.15	$[\mathrm{E2F1_{tot}}]$	1	[Casp9]	0.0588
$[\mathrm{Mdm2_{cp}}]$	0.9939	$[\mathrm{p21_{tot}}]$	0.188	$[\mathrm{Rb_p}]$	0	[Casp3]	0.0727

Supplemental Table S2: Parameter Values

Parameter	Description	Value	Reference
j_{DDp53}	Michaelis constant of DNA damage-dependent p53 activation	20	estimated
j_{DDm2}	Michaelis constant of DNA damage-dependent nuclear Mdm2 degration	22	estimated
k_{smdm20}	Basal induction rate of mdm2 mRNA	0.002	[1]
k_{smdm2}	p53-dependent transcription rate of mdm2	0.02	[1,3]
j_{smdm2m}	Michaelis constant of p53-dependent mdm2 mRNA production	1	[2,3]
k_{dmdm2m}	Degradation rate of mdm2 mRNA	0.04	estimated
k_{tmdm20}	MiR-192-dependent translation rate of mdm2 mRNA	0.2	estimated
j_{mir192}	Michaelis constant of miR-192-induced mdm2 mRNA translation repression	0.1	estimated
$k_{dmdm2n0}$	Basel degradation rate of nuclear Mdm2	0.03	[3,4]
$k_{dmdm2n1}$	DNA damage-dependent degradation rate of nuclear Mdm2	0.5	estimated
k_{dmdm2c}	Degradation rate of cytoplasmic Mdm2	0.03	[4]
k_{dpmdm2}	Dephosphorylation rate of cytoplasmic Mdm2	0.3	[3]
j_{dpmdm2}	Michaelis constant of Mdm2 dephosphorylation	0.1	[2,3]
k_{pmdm2}	Akt-dependent phosphorylation rate of cytoplasmic Mdm2	3.6	[3]
j_{pmdm2}	Michaelis constant of Akt-dependent Mdm2 phosphorylation	0.3	[2,3]
k_i	Nuclear import rate of $Mdm2_{cp}$	0.6	[2]
k_o	Nuclear export rate of $Mdm2_n$	0.9	[2]
$k_{smiR1920}$	Basal induction rate of miR-192	0.0008	estimated
$k_{smiR192}$	p53-dependent induction rate of miR-192	0.01	estimated
$j_{smiR192}$	Michaelis constant of p53-dependent miR-192 production	0.4	estimated
$k_{dmiR192}$	Degradation rate of miR-192	0.008	Estimated
k_{acp531}	DNA damage-dependent activation rate of p53	0.016	estimated
k_{acp530}	Basal activation rate of p53	0.0016	estimated
k_{dep53}	Deactivation rate of p53	0.008	estimated
k_{dp53p}	Mdm2-dependent degradation rate of $p53_p$	0.008	[1]
k_{sp53}	Production rate of p53	0.08	[1,3]
k_{dp53n}	Basal degradation rate of p53	0.04	[1,3]
k_{dp53}	Mdm2-dependent degradation rate of p53	0.48	[1]
j_{1p53n}	Michaelis constant of Mdm2-dependent p53 degradation	0.1	[2,3]
k_{acakt}	Phosphorylation rate of Akt	0.25	[2,3]
j_{acakt}	Michaelis constant of Akt phosphorylation	0.1	[2,3]
k_{deakt}	Dephosphorylation rate of Akt_p	0.1	[2,3]
j_{deakt}	Michaelis constant of Akt_p dephosphorylation	0.2	[2,3]
k_{p2}	Phosphorylation rate of PIP2	0.1	[2]

j_{p2}	Michaelis constant of PIP2 phosphorylation	0.2	[2]
k_{p3}	PTEN-dependent dephosphorylation rate of PIP3	0.5	[2]
j_{p3}	Michaelis constant of PIP3 dephosphorylation	0.4	[2]
PIP_{tot}	Total concentration of PIP2 and PIP3	1	[2,3]
Akt_{tot}	Total concentration of Akt	1	[2,3]
k_{sPTEN0}	Basal induction rate of PTEN	0.001	[5]
k_{sPTEN}	p53-inducible production rate of PTEN	0.06	[5]
j_{sPTEN}	Michaelis constant of p53-dependent PTEN production	2.5	[5]
k_{dPTEN}	Degradation rate of PTEN	0.01	[5]
k_{sp21m0}	Basal induction rate of p21 mRNA	6.8*E-5	estimated
k_{sp21m}	p53-dependent transcription rate of p21	0.0035	estimated
j_{sp21m}	Michaelis constant of p53-dependent p21 mRNA production	0.75	[5]
k_{dp21m0}	Basal degradation rate of p21 mRNA	7.5*E-5	estimated
k_{dp21m1}	MiR-22-dependent degradation rate of p21 mRNA	0.003	estimated
j_{22p21d}	Michaelis constant of miR-22-dependent p21 mRNA degradation	0.7	estimated
k_{tp210}	MiR-22-dependent translation rate of p21 mRNA	0.01	estimated
j_{22p21f}	Michaelis constant of miR-22-induced p21 mRNA translation repression	0.3	estimated
k_{dp21}	Degradation rate of p21	0.02	[6]
$k_{smiR220}$	Basal induction rate of miR-22	0.0006	estimated
k_{smiR22}	p53-dependent induction rate of miR-22	0.0075	estimated
j_{smiR22}	Michaelis constant of p53-dependent miR-22 production	1.9	estimated
k_{dmiR22}	Degradation rate of miR-22	0.006	estimated
$k_{asp21ce}$	Combining rate of p21 and CycE	2	estimated
$k_{dsp21ce}$	Dissociation rate of p21-CycE complex	0.1	estimated
k_{scyce0}	Basal induction rate of CycE	0.01	estimated
k_{scyce}	E2F1-dependent induction rate of CycE	0.15	estimated
j_{scyce}	Michaelis constant of E2F1-dependent CycE production	0.4	estimated
k_{dcyce}	Degradation rate of CycE	0.06	estimated
k_{asre}	Combining rate of Rb and E2F1	0.8	estimated
k_{dsre}	Dissociation rate of Rb-E2F1 complex	0.1	estimated
k_{se2f1}	Production rate of E2F1	0.0005	estimated
k_{de2f10}	Basal degradation rate of E2F1	6*E-5	[7]
k_{de2f11}	DNA damage-dependant degradation rate of E2F1	4.4*E-4	[7]
j_{DD2f}	Michaelis constant of DNA damage-induced E2F1 degradation repression	60	estimated
k_{prb}	Phosphorylation rate of Rb by CycE	0.4	estimated
j_{prb}	Michaelis constant of Rb phosphorylation by CycE	3.9	estimated
k_{dprb}	Dephosphorylation rate of Rb	0.2	estimated

j_{dprb}	Michaelis constant of Rb dephosphorylation	1	estimated
$[Rb_{tot}]$	Total concentration of Rb	2	estimated
k_{sbax0}	Basal induction rate of Bax	0.002	estimated
k_{sbax}	p53-dependent induction rate of Bax	0.06	estimated
j_{sbax}	Michaelis constant of p53-dependent Bax production	2.3	estimated
k_{dbax}	Degradation rate of Bax	0.02	estimated
$k_{accytoc0}$	Basal release rate of mitochondrial cytochrome c	0.001	[2]
$k_{accytoc1}$	Bax-dependent release rate of mitochondrial cytochrome c	1.5	[2]
j_{cap3bx}	Michaelis constant of caspase-3 dependent cytochrome c release	0.2	[2]
$k_{decytoc}$	Mitochondrial influx rate of cytochrome c	0.05	[2]
$Cytoc_{tot}$	Total concentration of cytochrome c	3	[2]
$k_{sapaf10}$	Basal induction rate of Apaf-1	0.001	[5]
k_{sapaf1}	E2F1-dependent induction rate of Apaf-1	0.25	[5]
j_{sapaf1}	Michaelis constant of E2F1-dependent Apaf-1 production	0.8	[5]
k_{dapaf1}	Degradation rate of Apaf-1	0.1	[5]
$k_{acapops}$	Rate of Apaf-1 and cytochrome c assembling into apoptosome	0.7	estimated
$k_{deapops}$	Deactivation rate of apoptosome	0.5	[5]
$Casp9_{tot}$	Total concentration of caspase-9	3	[5]
$k_{accasp90}$	Basal activation rate of caspase-9	0.001	[5]
$k_{accasp91}$	Caspase-3- and Apoptosome-dependent activation rate of caspase-9	3	[5]
j_{casp3}	Michaelis constant of caspase-3-dependent caspase-9 activation	0.3	estimated
j_{apops}	Michaelis constant of apoptosome-dependent caspase-9 activation	0.35	estimated
$k_{decasp9}$	Deactivation rate of caspase-9	0.05	[5]
$Casp3_{tot}$	Total concentration of caspase-3	3	[5]
$k_{accasp30}$	Basal activation rate of caspase-3	0.001	[5]
$k_{accasp31}$	Caspase-9-dependent activation rate of caspase-3	0.5	estimated
j_{casp9}	Michaelis constant of caspase-9-dependent caspase-3 activation	0.3	estimated
$k_{decasp3}$	Deactivation rate of caspase-3	0.07	[5]

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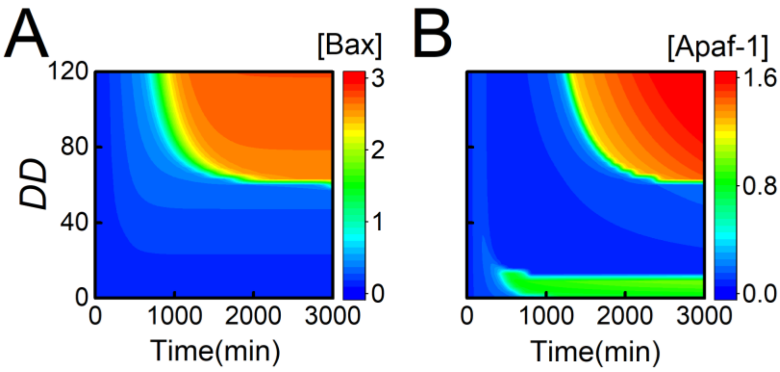

Figure S1: Heat map of [Bax] (*A*) and [Apaf-1] (*B*) as a function of Time and *DD*.